Current Chemistry Letters 11 (2022) 29–42

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Current Chemistry Letters

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An overview on synthesis and reactions of coumarin based compounds

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C H R O N I C L E

Article history:
Received June 23, 2021
Received in revised form
July 18, 2021
Accepted September 29, 2021
Available online
September 29, 2021

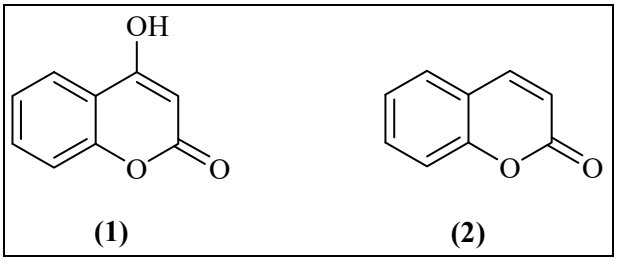
Keywords:
Coumarins
Heterocycles
Structures
Herbicides

A B S T R A C T

Oxygen-containing heterocycles are largely distributed in natural and synthetic compounds. Coumarins are among the most famous heterocycles which possess one oxygen atom in their rings. Coumarins are classified as multifunctional scaffold and are used as anti-oxidant reagents, anti-inflammatory, anti-microbial, anti-fungal, anti-HIV active, analgesic, anti-histaminic, insecticides, dyes, herbicides, sensitizers, perfumes, cosmetics and food additives. Due to their diverse applications in industrial and pharmaceutical fields, many chemists have given significant interest to these compounds. Herein, the review highlights various methods for the synthesis and interactions of coumarin moiety as one of the most efficient categories of heterocycles.

1. Introduction

Coumarins have been known as fragrance materials in perfumes for a rather long time, because of their sweet smell. Naturally occurring coumarins are known in about 700 structures in more than 100 plant families,[1] and the number of structures still increases.



(1) **(2)**

Fig. 1. Structures of 4-hydroxycoumarin **(1)** and coumarin **(2)**.

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doi: 10.5267/j.ccl.2021.009.007

The first important research about coumarins and its derivatives were about their potential toxicities to both animals and plants, such as phototoxic, photosensitizing.[1] But these properties are also considered as therapeutic potentials.[2] Now they are widely used in pharmaceutics because of their biological activities. Additionally, coumarin derivatives have been used as antioxidant reagents,[3] dyes,[4] insecticides,[5] sensitizers,[6] herbicides, food additives, perfumes, and cosmetics (**Fig. 1**).

4-Hydroxycoumarins are among the most important coumarin derivatives, because they contain a wide range of biological activities. They can be anticoagulant,[7] antibacterial,[8] anti-HIV active,[9] and anti-tumoral.[10] The nucleus of 4-hydroxycoumarin is very susceptible to electrophilic substitution,[11] so they are very easy synthesized and substituted by other functional groups to enhance their biological activities.

If 4-hydroxycoumarin is substituted by phenyl, benzyl or phenoxy groups at position 3, the compound is a HIV-1 protease inhibitor.[12] If the substituent is an acyl group, the compound can be used as an insecticide.[5] The pharmacological activities of 3-substituted 4-hydroxycoumarins are also depended on the tautomeric conversions.

Tautomeric forms of 3-substituted-4-hydroxy coumarin: the structure of 3-substituted-4-hydroxy coumarin consists of a benzene ring fused with a pyrone ring. The carbonyl group is attached at C-2 position, substitution group in position 3 and hydroxyl group in position 4. Three major tautomeric forms of 3-substituted-4-hydroxy coumarin can be formed and are presented in the following scheme (**Fig. 2**).[13,14]

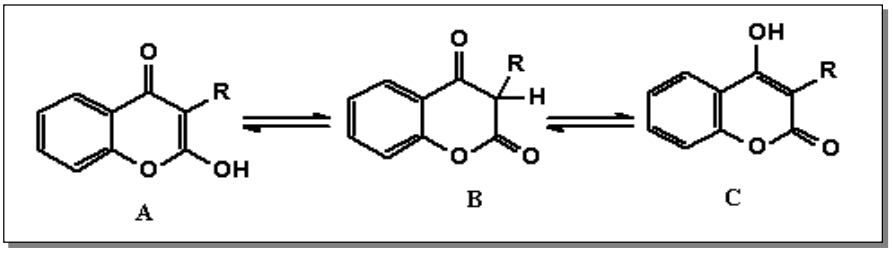
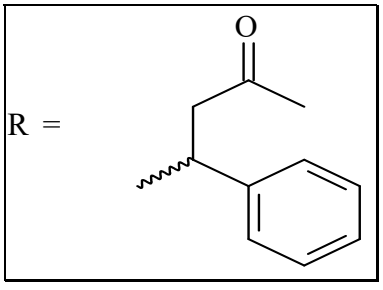


Fig. 2. Tautomeric forms of 3-substituted-4-hydroxy coumarin

The unstable tautomeric form 3-substituted-4-oxohydrocoumarin **(B)** of Wafarin can inhibit the vitamin K epoxide cycle and can therefore be used for anticoagulant[15] where as R = 3-oxo-1-phenylbutyl-.



3-Acyl-4-hydroxycoumarin **(3)** shows different biological activities for various acyl groups. With a short-chain acyl group, the compound shows high ovicidal rates, but the longer the chain, the lower is the activity. If the acyl group in position 3 is long-chained (10 or more carbons) and contains a terminal ethylene bond, it shows a high antibacterial activity.[16]

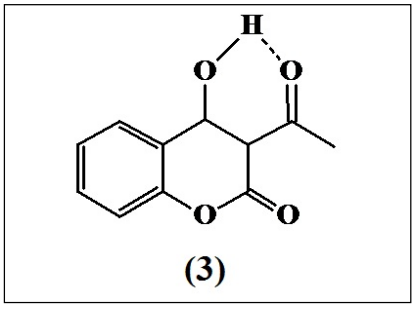


Fig. 3. Structure of 3-acyl-4-hydroxycoumarin

The strong hydrogen bond in 3-acyl-4-hydroxycoumarin **3** can be shown under X-ray diffraction.[17] 3-acetyl-4-hydroxycoumarin shows different tautomeric forms in different solvents.[18] It performs the 3-acetyl-4-hydroxycoumarin form (A) in non-polar solvents (n-hexane, CCl_4), while it exists in the 3-(α-hydroxy)ethylidene-4-oxohydrocoumarin form (B) in protic solvents (methanol, ethanol) following (**Fig. 4**).

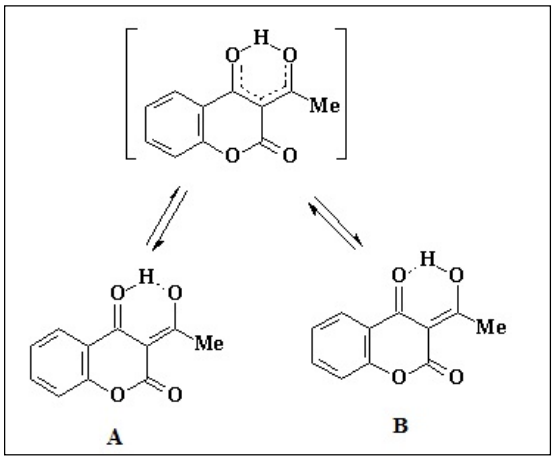


Fig. 4. Hydrogen bond in 3-acetyl-4-hydroxycoumarin

2. Some synthetic routes of coumarins

2.1 From phenols.

In 1960 Shah et al.[19] concluded that there were three principal methods for the synthesis of 4-hydroxycoumarins. Among these, one synthetic route leads first to 3-substituted 4-hydroxycoumarins and this intermediate can afterwards be converted to the corresponding 4-hydroxycoumarin. It is the condensation reaction of acetyl salicyloyl chlorides with acetoacetic, cyanoacetic or malonic ester.

Shah et al. found a new and simple process in which a phenol is treated with an equimolar proportion of a malonic acid in the presence of a mixture of double to triple molar amount of each anhydrous zinc chloride and phosphorus oxychloride as condensing agent. They condensed successfully substituted malonic acids, e.g. *n*-octylmalonic acid, with phenol and received good yields of the corresponding 3-substituted 4-hydroxycoumarins, f. ex. 3-*n*-octyl-4-hydroxycoumarin (**Fig. 5**).

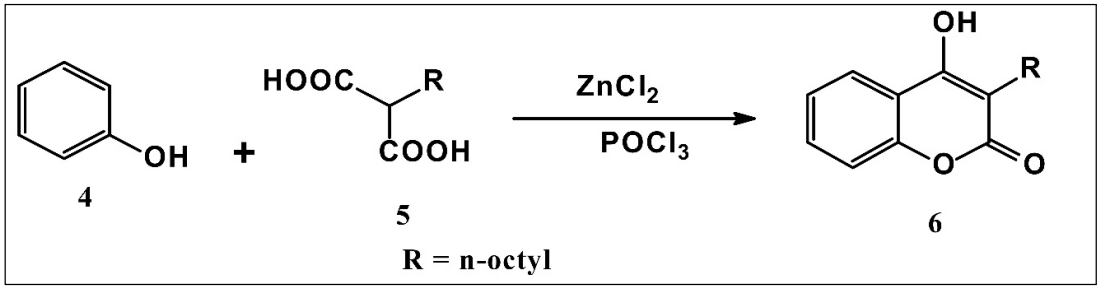


Fig. 5. Reaction of phenol and substituted malonic acid to form 3-substituted 4-hydroxycoumarin

Condensation of phenol **(4)** with 3,3-dichloroallylmalonic acid **(5)** (R=-CH_2-CH=CCl_2) in the presence of phosphorus oxychloride and zinc chloride, resulting in the formation of 3-(3,3-dichloroallyl)-4-hydroxycoumarin **(6)** (**Fig. 6**).[20]

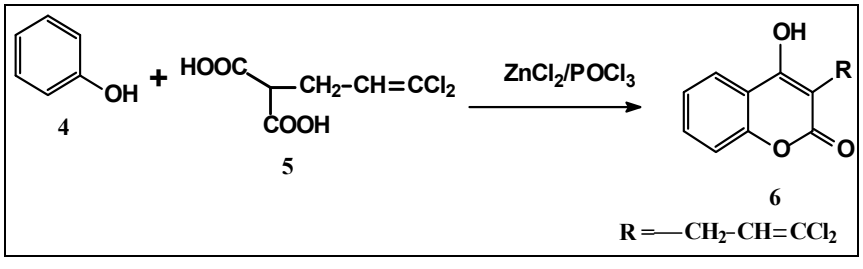


Fig. 6. Synthesis of 3-(3,3-dichloroallyl)-4-hydroxycoumarin **(6)**.

Friedel-Crafts condensation of substituted malonic acid derivative **(5)** with phenol **(4)** to produce various 3-substituted 4-hydroxycoumarin compounds.[19] In this study, a photoaffinity derivative of 4-hydroxycoumarin **(8)** was synthesized by the introduction of a p-azidobenzyl group at the 3-position through the condensation of p-nitrobenzylmalonic acid with phenol followed by reductive to give **(7)** . The latter was converted to the azido compound **(8)** (**Fig. 7**).[21]

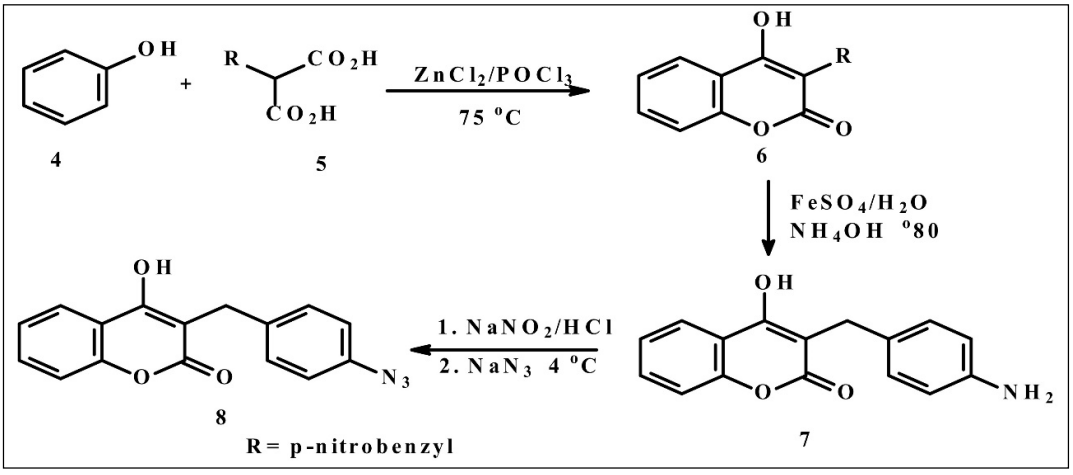


Fig. 7. Synthesis of the azido compound 3-(4-azidobenzyl)-4-hydroxy-2*H*-chromen-2-one **(8)**

The malonates **(9a-c)** were prepared from commercially available phenols in good yield according to the literature procedure.[22] Treatment of compounds **(9a-c)** under neat conditions with $AIC1_3$ for 10-15 h at 180°C gave **(10a-c)** as a sole product. The side chain can be removed by simply heating of **(10c-e)** in 90% H_2SO_4 for 2 hr to give the desired fluorinated 4-hydroxyl coumarins **(1c-e)** as the sole product. This reaction goes through **(11)** as an intermediate which then can be further deacetylated to **(1c-e)** (**Fig. 8**).[23]

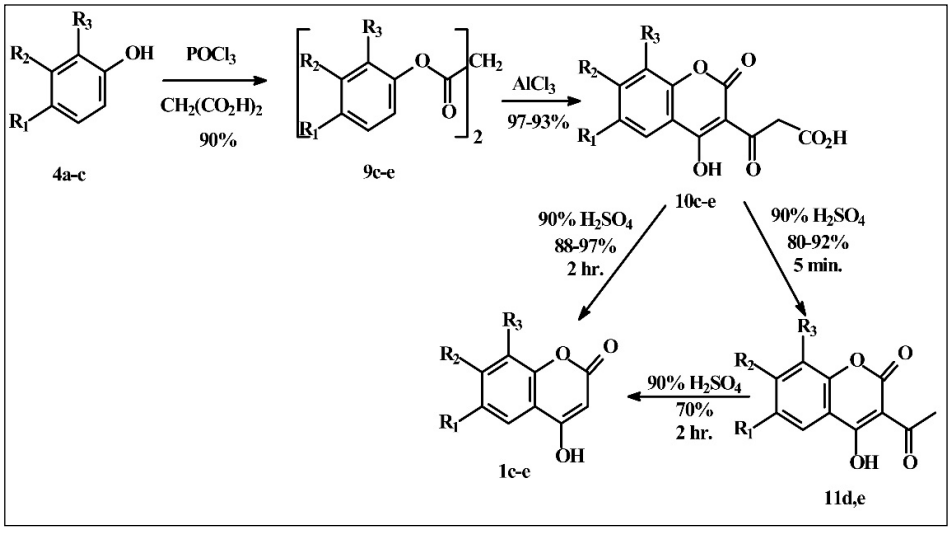


Fig. 8. Synthesis of fluorinated 4-hydroxyl coumarins **(1c-e)**

Mentzer et. al.[24] reported that, the thermal condensation of monosubstituted alkyl or aryl of malonic esters with phenols lead to the formatoion of various derivatives of 4-hydroxycoumatin substituted at position 3. Aleksyuk et al.[25-27] reported that in similar manner synthesis of 4-hydroxycoumarin **(6)** substituted at position 3 or in aromatic ring with benzyl, o,m,p-benzyl or a-naphthylmethyl groups (**Fig. 9**).

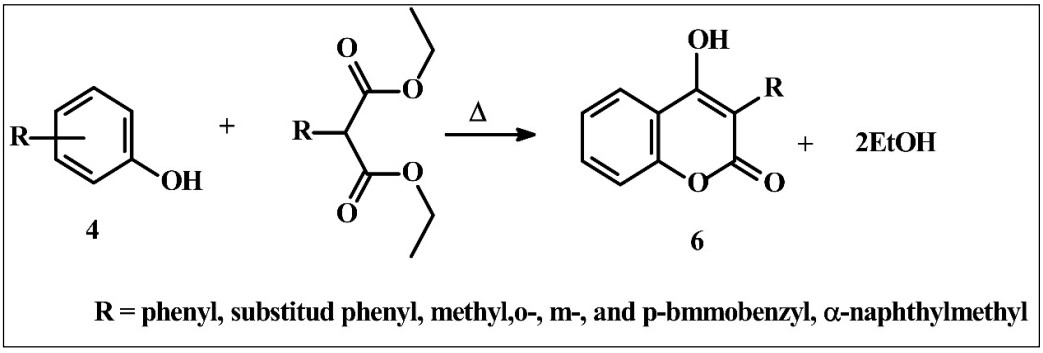


Fig. 9. Synthesis of 4-hydroxycoumarin **(6)**

Malonic acid monophenyl ester **(13a)** and phenylsulfanylcarbonyl acetic acid **(13b)** were synthesized from the reaction of phenol or thiophenol **(4a, b)** with Meldrum's acid **(12)** by stirring at 90 ºC for 4 h. 4-hydroxycoumarin **(1a)** were prepared by heating **(13a)** with Eaton's reagent (phosphorus pentoxide solution in methanesulfonic acid) at 70 ºC with stirring vigorously, while 4-hydroxythiocoumarin **(1b)** was prepared by stirring **(13b)** vigorously at 120 ºC in polyphosporic acid (PPA) (**Fig. 10**).[28]

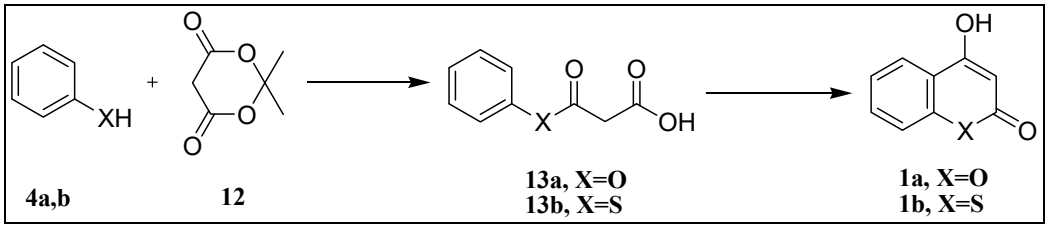


Fig. 10. Synthesis of 4-hydroxycoumarin **(1a)** and 4-hydroxythiocoumarin **(1b)**

2.2 From dihydroxyacetophenones.

G. Roma et al.[29] reported synthesis of 4- hydroxy coumarin by the reaction of the dihydroxy acetophenones **(14a–c)** with proper alkyl iodides in dry acetone in the presence of anhydrous K_2CO_3, at refluxing temperature to give the corresponding alkoxy derivatives **(15a–c)**. The cyclocondensation of **(15a-c)** with diethyl carbonate in dry toluene room temperature in the presence of potassium tert-butoxide, afforded the 4-hydroxycoumarins **(16a-e)**. The treatment of these compounds with a large excess of piperazine at 160°C, good yields of the corresponding 4-(1-piperazinyl) coumarins **(17a-e)** were obtained (**Fig. 11**).

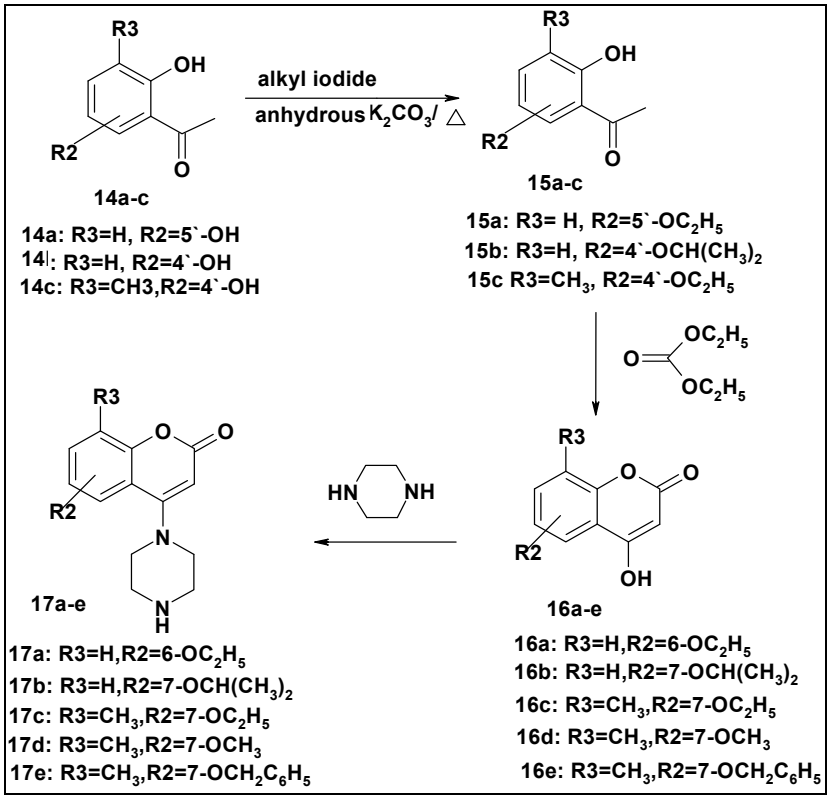


Fig. 11. Synthesis of 4-(1-piperazinyl) coumarins **(17a-e)**

A new carbamoyl Baker-Venkataraman rearrangement allows a general synthesis of substituted 4-hydroxycoumarins **(20)** in good overall yields starting from ortho-acylated arylcarbamates **(18)**. The intermediate arylketones **(19)** are efficiently prepared via a Directed *ortho* Metalation - Negishi cross coupling protocol from arylcarbamates. The overall sequence provides a regiospecific anionic Friedel-Crafts complement for the construction of *ortho*-acyl phenols and coumarins (**Fig. 12**).[30]

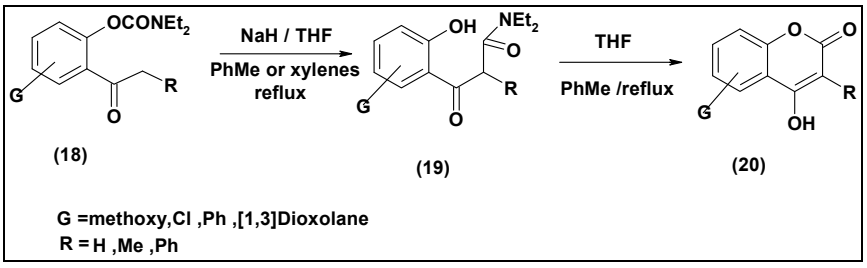


Fig. 12. Synthesis of substituted 4-hydroxycoumarins **(20)**.

Acetophenone **(21a)** was treated with the appropriate carbocyclic ketone in the presence of pyrrolidine to result in the spirochromanones **(22a–c)**. These compounds were converted to the corresponding mesylates **(23a–c)**, which were subjected to borohydride reduction to provide the spirochromanols **(24a–c)**. Dehydration of compounds **(24a–c)** in the presence of an acidic catalyst yielded the mesylates **(25a–c)** and the mesyl group was then removed in alkaline media to provide the spirochromenes **(26a–c)**. These spirochromenes were first treated with Meldrum's acid and the resulting esters **(27a–c)** were ring-closed in the presence of trifluoroacetic anhydride to result in the 4-hydroxychromenes **(28a–c)** (**Fig. 13**).[31]

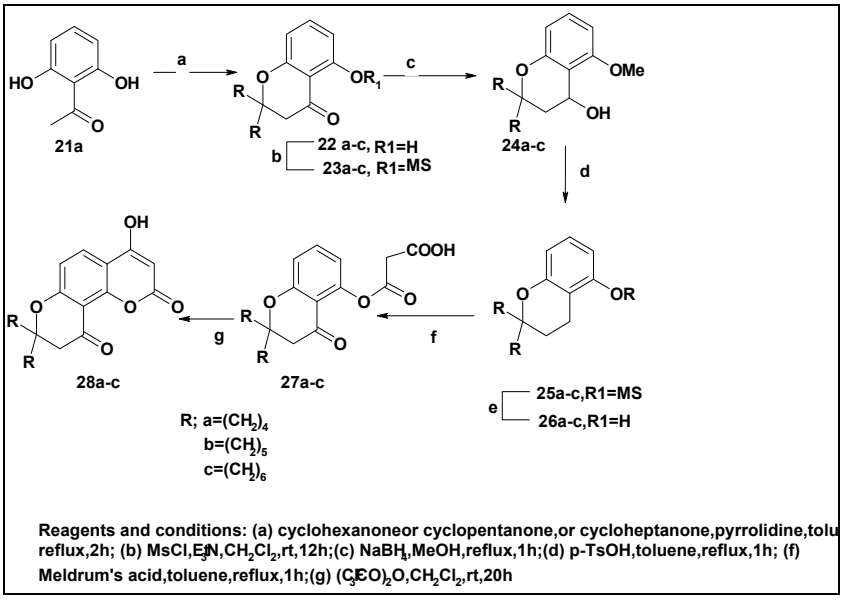


Fig. 13. Synthesis of 4-hydroxychromenes **(28a–c)**

A quantitative yield of **(30)** was obtained, when ethyl chloroformate was added to **(29)** in pyridine solution. Treatment of **(30)** with potassium carbonate in toluene 4-Hydroxy-naphthocoumarin **(31)** (**Fig. 14**).[32]

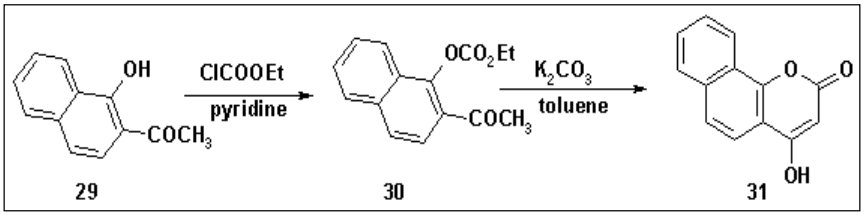


Fig. 14. Synthesis of 4-Hydroxy-naphthocoumarin **(31)**

3-(5-Ethoxycarbonyl-2-furyl)-6-ethyl-4-hydroxy-7-methoxycoumarin **(34)** was prepared via Claisen condensation of α-(5-ethoxycarbonyl-2-furyl)-5-ethyl-2-hydroxy-4-methoxyacetophenone **(32)** in dry diethyl carbonate in the presence of sodium tert-butanolate in an atmosphere of argon to afforded hydroxycoumarins **(33a-c)**, which were acylated affording hydroxycoumarins **(34 a-I)** (**Fig. 15**).[33]

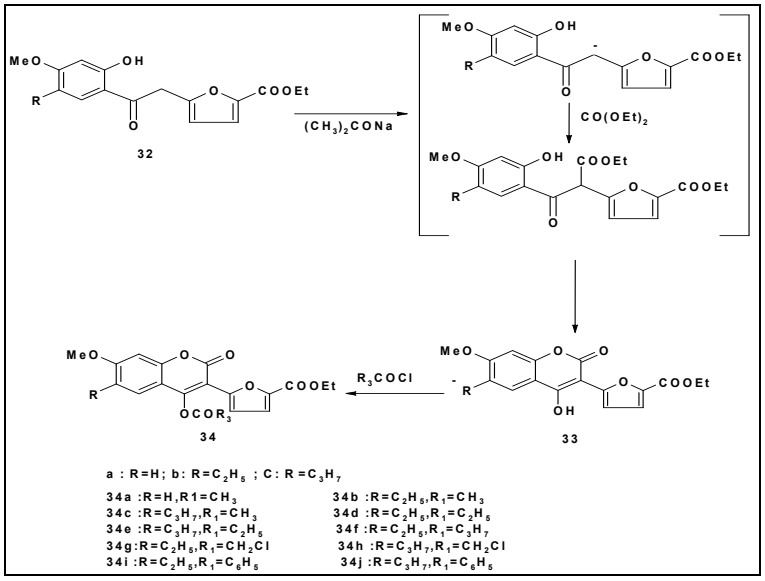


Fig. 15. Synthesis of hydroxycoumarins **(34 a-I)**

2.3 From Salicylic *acid derivatives*.

4-Hydroxycoumarins **(37)** was prepared by treatment of α-halocarboxylic acid esters of salicylaldehyde, *o*-hydroxyacetophenone, and methyl salicylate **(35)**, with sodium or lithium telluride (**Fig. 16**).[34]

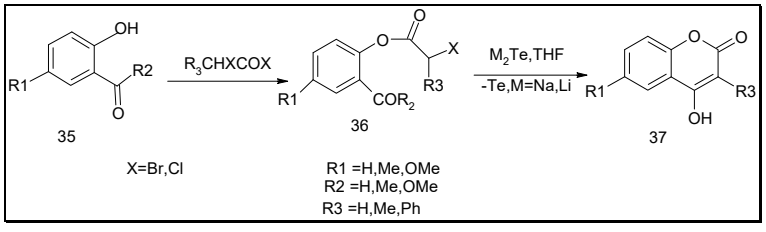


Fig. 16. Synthesis of 4-Hydroxycoumarins **(37)**

3 Reactions of coumarin compounds

3.1 Etherification

4,6-Dihydroxycoumarin **(38)** was methylated with dimethyl sulphate in potassium hydroxide solution to afford 4,6-dimethoxycoumarin **(39)** (**Fig. 17**).[35]

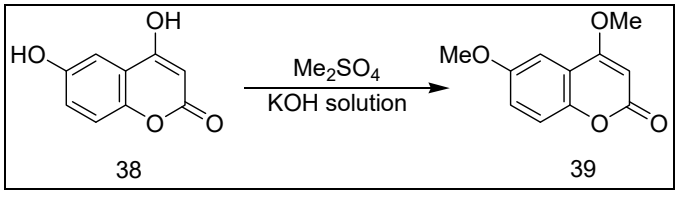


Fig. 17. Synthesis of 4,6-dimethoxycoumarin **(39)**.

The reaction of 4-hydroxycoumarin **(1)** with primary amines and formaldehyde proceeded very rapidly, the 3-substituted aminomethyl-4-hydroxycoumarins were formed **(40)** (**Fig. 18**).[36]

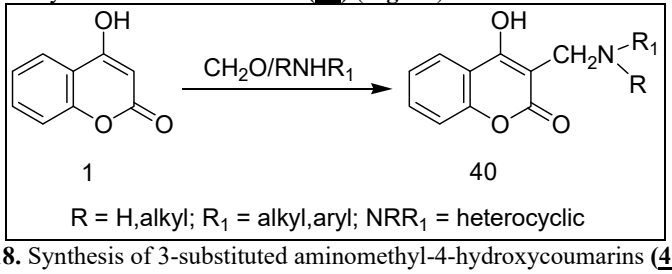


Fig. 18. Synthesis of 3-substituted aminomethyl-4-hydroxycoumarins **(40)**

3.2 Acylation

Acylation of 4-hydroxycoumarin was accomplished using acetyl chloride in pyridine in the presence of catalytic amount of piperideine to afford 3-acetyl-4-hydroxycoumarin **(3)** (**Fig. 19**).[37]

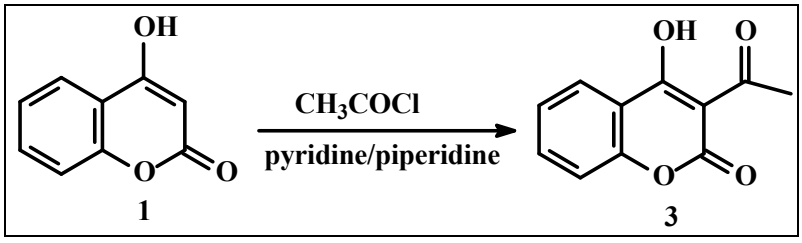


Fig. 19. Synthesis of 3-acetyl-4-hydroxycoumarin **(3)**

Cravotto et al.[16] prepared a series of 3-acyl-4-hydroxycoumarins **(3)** by reacting 4-hydroxy-coumarins with several long-chain acyl chlorides under sonochemical conditions (**Fig. 20**).

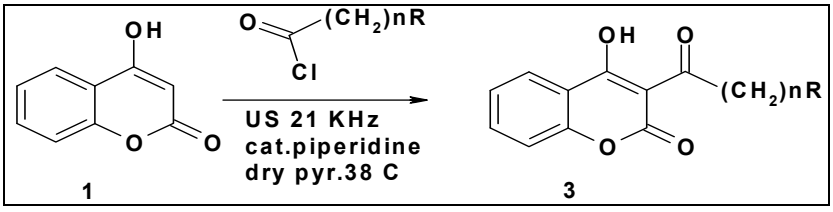


Fig. 20. Synthesis of 3-acyl-4-hydroxycoumarins **(3)**

3.3 Miscellaneous reactions

Furocoumarins **(41)** differentially substituted on the five-membered ring was obtained starting from 4-hydroxycoumarin **(1)**. The idea arose from the using the double electrophile α-haloketones **(42)** with 4-hydroxycoumarin **1** in glacial $AcOH/AcONH_4$ or piperidine in refluxing toluene/EtOH (4:1) to produced the expected cycloadducts **(41)** in good yield (70–77%).

In entry **f**, the desired cycloaddition failed: desyl chloride **(42f)** and **1** were recovered unreacted. This failure can be attributed to the presence of the bulky phenyl substituent in the α-position. In entry **g**, however, the reaction of **1** with **(42g)** under similar conditions ($AcOH/AcONH_4$, refluxing toluene/EtOH) gave the dihydrofuran derivative **(43)** in high yield (90%) (**Fig. 21**).[38]

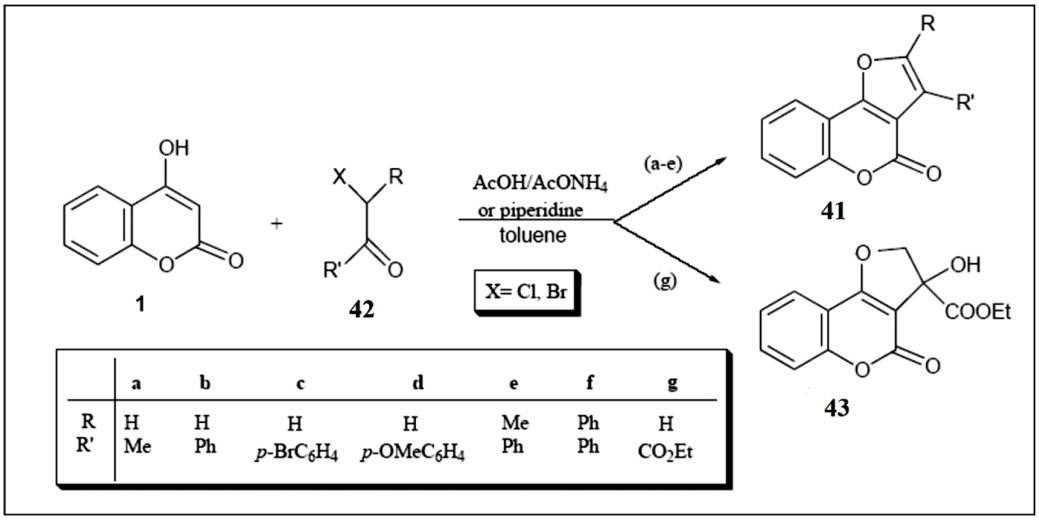


Fig. 21. Synthesis of dihydrofuran derivative **(43)**

4-hydroxycoumarin **(1)** was reacted with phenylglyoxal **(44)** in the presence of 1,4-diazabicyclo[2.2.2]octane(dabco)$[CH_3COO]_2$ at room temperature to give **(45)** which upon irradiation by microwave in the presence of $POCl_3$ the desired product **(46)** was obtained (**Fig. 22**).[39]

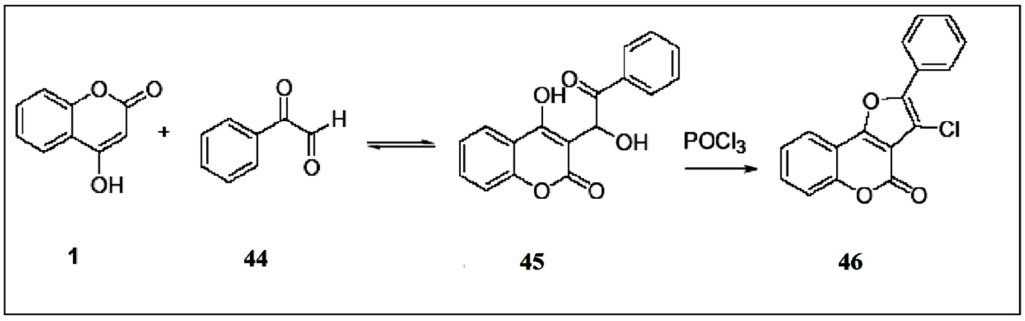


Fig. 22. Synthesis of compound **(43)**

Condensation of 4-hydroxycoumarin **(1)** with aryl (alkyl) amines followed by treatment with sodium hydroxide solution afforded 4-aryl(alkyl) aminocoumarins **(47)**.

Treatment of arylaminocoumarins **(47)** with phosphorusoxychloride in DMF affording benzopyrano[4,3-b]quinolines **(48)**. In similar manner treatment of alkylaminocoumarin with phosphorusoxychloride in DMF affording 4-alkylamin-3-formylcoumarins **(49)** (**Fig. 23**).[40]

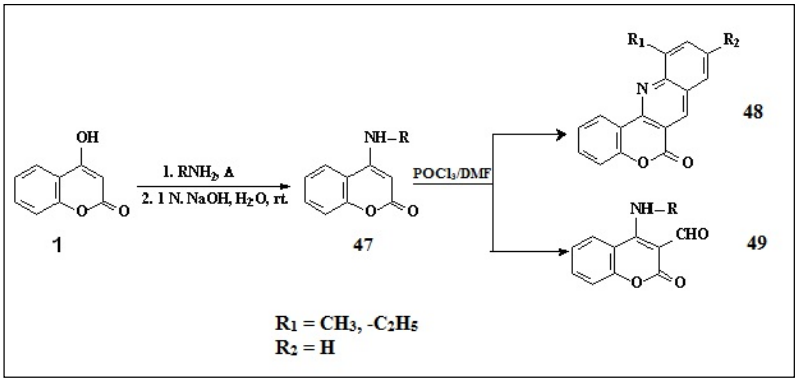


Fig. 23. Synthesis of compounds **(47-49)**

Ultrasound irradiation of 4-Chloro-3-formylcoumarin **(50)** and aniline derivatives **(51)** in ethanol lead to the formation of the fused chromeno - quinolines **(52)** in good yields (**Fig. 24**).[41]

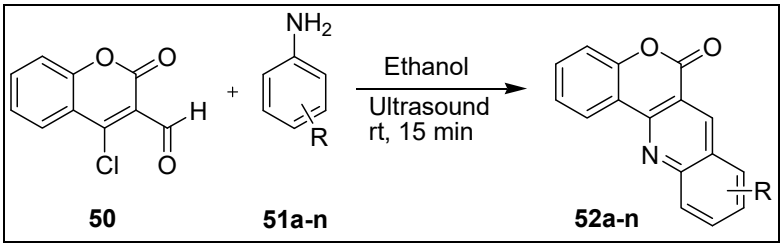


Fig. 24. Synthesis of the fused chromeno - quinolines **(52)**

The 3-benzylidenecoumarins **(53)** were prepared as shown in scheme. The Knovenagel condensation of 4-hydroxycoumarins **(1a–b)** with substituted benzaldehydes in pyridine gave compounds **(53)** in only one diastereoisomeric form (*Z*) (**Fig. 25**).[42]

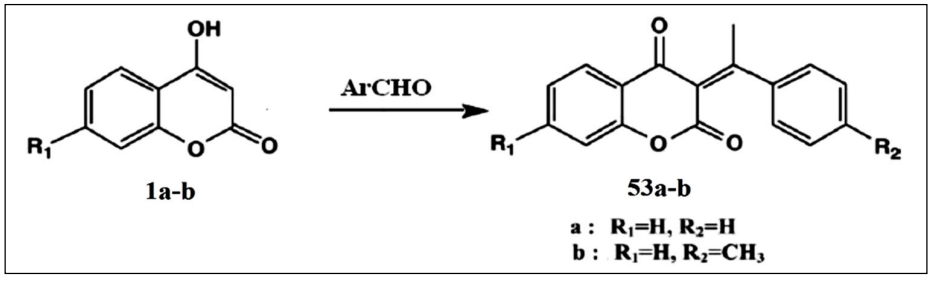


Fig. 25. Synthesis of the 3-benzylidenecoumarins **(53)**

3,3′-(4-dimethylaminobenzylidene)-bis-(4-hydroxycoumarin) **(54)** was synthesized by the reaction of 4-hydroxycoumarin with 4-dimethylaminobenzaldehyde, and its chemical structure was determined by X-ray single-crystal diffraction (**Fig. 26**).[43]

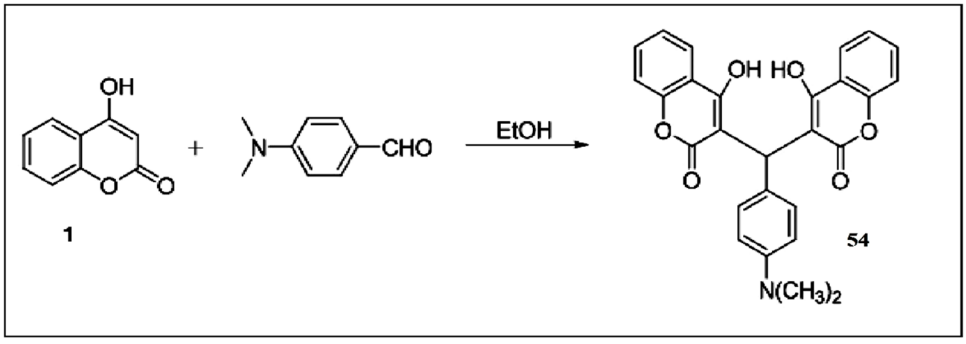


Fig. 26. Synthesis of 3,3′-(4-dimethylaminobenzylidene)-bis-(4-hydroxycoumarin) **(54)**

A series of 6H,7H-chromeno[3`,4`:4,5]thieno[3,2-b]indol-6-ones **(55a-l)**, bearing thieno[3,2-b]indole and coumarin parts in their fused molecules, were readily prepared using one-pot procedure based on reaction of 3-aminothieno[3,2-c]coumarins, in situ formed from 3-aminothieno[3,2-c]coumarin-2-carboxylates,with arylhydrazines according to the Fischer indole synthesis (**Fig. 27**).[44] This work confirms that the chemistry of functionalized heterocyclic compounds is widely known, which is reflected in many papers that have been published before.[45-90]

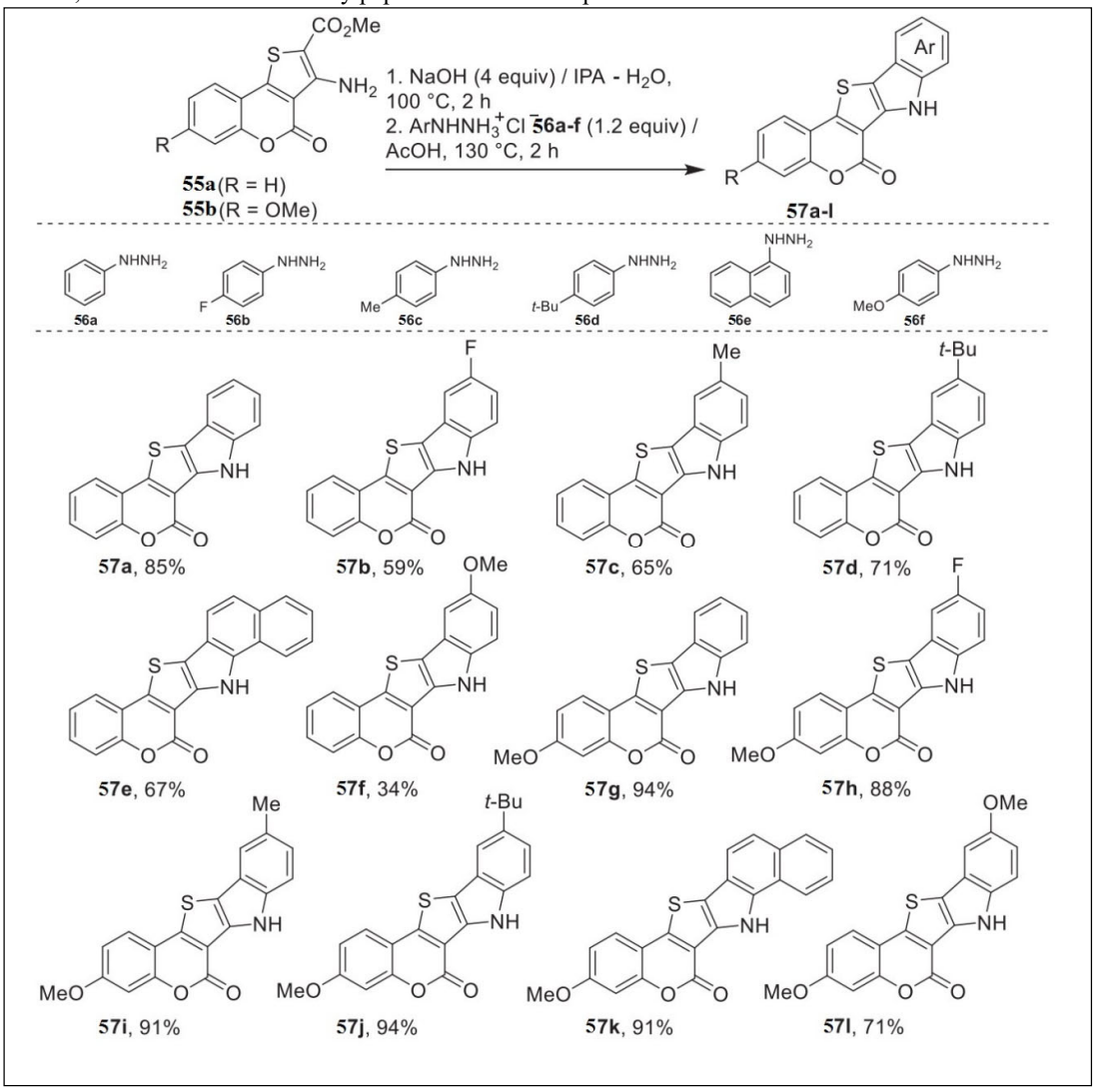


Fig. 27. Synthesis of 6H,7H-chromeno[3`,4`:4,5]thieno[3,2-b]indol-6-ones **(55a-l)**

4. Conclusions

Coumarins are an important class of compounds of natural and synthetic origin. Due to their various pharmacological effects, coumarin compounds are of great importance. These biological properties, in particular, make coumarin compounds more attractive for investigation as new medicinal agents. Future goals of this research field include emphasizing the state of this scaffold and its role in the design and synthesis of more advanced classes of structural units for various medical and industrial applications. In addition to attempting to study the relationship between structure and active biological activity, which aims to understand the mechanism of action of the most biologically active compounds in inhibiting and treating most diseases.

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